BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 3 :
A61K 9/14, 9/50

A1

(11) International Publication Number: WO 84/ 02270

(43) International Publication Date: 21 June 1984 (21.06.84)

(21) International Application Number: PCT/SE83/00440

(22) International Filing Date: 9 December 1983 (09.12.83)

(31) Priority Application Number: 57/218134

(32) Priority Date: 13 December 1982 (13.12.82)

(33) Priority Country: JP

(71) Applicant *(for all designated States except US)*: AB LEO [SE/SE]; Box 941, S-251 09 Helsingborg (SE).

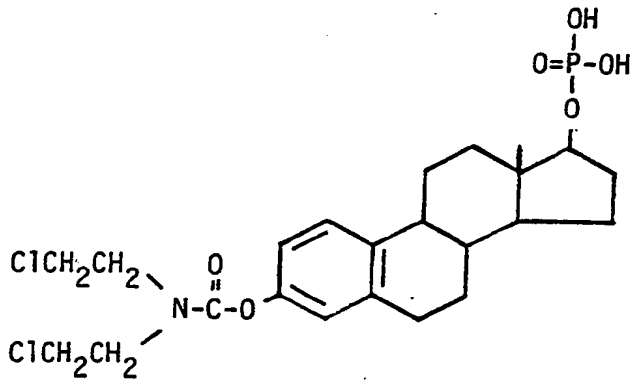
(71)(72) Applicants and Inventors: YOSHIDA, Masaru [JP/JP]; 96-4, Ohashi-Machi, Takasaki-Shi, Gunma 370 (JP). ASANO, Masaharu [JP/JP]; 2-15-19, Kataoka-Machi, Takasaki-Shi, Gunma 370 (JP). KAETSU, Isao [JP/JP]; 170-1, Namiecho, Takasaki-Shi, Gunma 370 (JP). NAKAI, Katsuyuki [JP/JP]; 4-7, Shimokawa-Cho, Maebashi-Shi, Gunma 379-21 (JP). YAMANAKA, Hidetoshi [JP/JP]; 1-14-22, Takahanadai, Maebashi-Shi, Gunma 370-01 (JP). SHIDA, Keizo [JP/JP]; 3-38-27, Showa-Machi, Maebashi-Shi, Gunma 371 (JP).

(74) Agent: THYLÉN, Eva; AB Leo, Box 941, S-251 09 Helsingborg (SE).

(81) Designated States: AT (European patent), BE (European patent), CH (European patent), DE (European patent), FR (European patent), GB (European patent), LU (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.

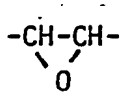
(54) Title: MICROFINE PARTICLES HAVING TARGET-SEEKING PROPERTIES



I

(57) Abstract

Target-seeking microfine particles wherein estradiol-3N-bis-(2-chloroethyl)-carbamate 17β-phosphate of formula (I) is bound to the reactive site of a carrier particle having at least one functional group selected from the group consisting of -CHO, -Cl, $-NH_2$, -COOH, -OH, -NCO and



Optionally, a cancer control agent is entrapped in the microfine particles.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

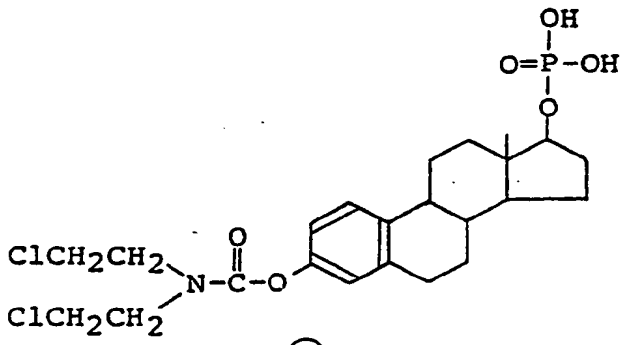
AT	Austria	**LI**	Liechtenstein
AU	Australia	**LK**	Sri Lanka
BE	Belgium	**LU**	Luxembourg
BR	Brazil	**MC**	Monaco
CF	Central African Republic	**MG**	Madagascar
CG	Congo	**MR**	Mauritania
CH	Switzerland	**MW**	Malawi
CM	Cameroon	**NL**	Netherlands
DE	Germany, Federal Republic of	**NO**	Norway
DK	Denmark	**RO**	Romania
FI	Finland	**SE**	Sweden
FR	France	**SN**	Senegal
GA	Gabon	**SU**	Soviet Union
GB	United Kingdom	**TD**	Chad
HU	Hungary	**TG**	Togo
JP	Japan	**US**	United States of America
KP	Democratic People's Republic of Korea		

Microfine particles having target-seeking properties

Detailed Description of the Invention:

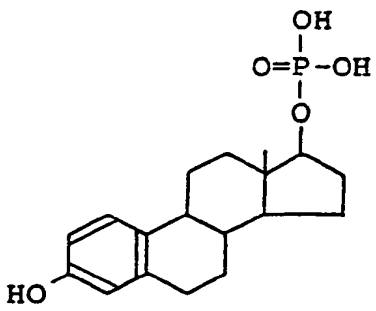
The present invention relates to microfine particles having the target-seeking property and being capable of slow release of cancer control agents. More particularly, the invention relates to microfine particles that ensure the target-seeking property and atrophic action of Estracyt® and which are capable of slowly releasing cancer control agents.

Estracyt® was first synthesized by the Research Laboratory of AB Leo, Sweden, in 1966. Its chemical name is estradiol-3N-bis-(2-chloroethyl)-carbamate-17β-phosphate. Estracyt® has the following formula (I):



(I)

More specifically, Estracyt® consists of estradiol-17β-phosphate of formula (II) to which nitrogen mustard of formula (III) is attached at 3N-position by the carbamate:



(II)

$$ClCH_2CH_2 \\ ClCH_2CH_2 \rangle N-H \qquad (III)$$

Estracyt® has been reported to have excellent cancer controlling effect against progressive prostatic cancer. See, for example, A. Koga, H. Yamanaka, K. Imai, K. Nakai, Y. Matsumura, H. Uehara and K. Shida; Clinical trial of estramustine phosphate (Estracyt®) for prostatic carcinoma, Acta Urol. Japon. 26, 369-376 (1980). When administered sytemically, Estracyt® exhibits the localized cancer controlling action in the tissue of prostatic cancer by virtue of the synergistic effect of estradiol-17β-phosphate (II) and nitrogen mustard (III). One of the important features of Estracyt® is its causing minimum side effects. However, in clinical fields, Estracyt® is administered daily in 560 mg per adult (by oral route) or 300-400 mg per adult (injection) (H. Yamanaka, K. Imai, H. Yuasa and K. Shida; The Prostate Supplement, 1 95-102 (1981)). Estracyt® administered in such high doses may cause estrogenic side effects such as hepatic, gastrointestinal and cardiac disorders.

Estracyte® is known to bind specifically with the prostatic protein produced from prostate-related cells (B. Forsgrem, J-Å Gustafsson, Å. Pousette and B. Högberg; Binding characteristics of major protein in rat ventral prostate cytosol that interacts with estramustine, a nitrogen mustard derivative of 17β-estradiol, Cancer Res., 39 5155-5164 (1979)). Noting this unique feature of Estracyt®, the present inventors started experiments on binding Estracyt® chemically with microfine particles or micro-

capsules. The inventors thought that when microfine particles or microcapsules chemically binding with Estracyt^{R} (these particles and capsules are sometimes collectively referred to as Estracyt^{R} bound microfine particles hereunder) were introduced into the blood circulation, the Estracyt^{R} bound microfine particles would accumulate in prostate related organs, namely, ventral prostate, dorsolateral prostate, seminal vesicle, testicle and adrenal body. If this was the case intensive treatment of prostate related organs would become possible and topical therapy much more effective against cancers than oral administration and injection could be realized.

As a result of various studies made on the basis of this recognition the present inventors have developed microfine particles having specific functional groups to which Estracyt^{R} is bound. These particles retain the ability of Estracyt^{R} to be taken up by prostate-related organs and to contract their size. This unique capability of Estracyt^{R} is hereunder referred to as its target-seeking property.

The present inventors further developed their studies and bound Estracyt^{R} chemically or physically to microfine particles having specific functional groups which had cancer control agents entrapped therein. The resulting microfine particles retained the target-seeking property of Estracyt^{R} and were capable of slowly releasing the entrapped cancer control agent. In the following pages these particles are referred to as "Estracyt^{R} bound cancer control agent entrapping, slow-

release microfine particles". Unless otherwise noted, these particles and the "Estracyt® bound microfine particles" are collectively referred to as "Estracyt® bound microfine particles" hereunder.

Therefore, one object of the present invention is to provide Estracyt® bound microfine particles and a process for producing the same.

Another object of the present invention is to provide Estracyt® bound, cancer control agent entrapping, slow-release microfine particles and a process for producing the same.

A further object of the present invention is to provide a method of treating prostate cancer using either type of the Estracyt® bound particles.

In our efforts to bind Estracyt® chemically to microfine particles, the present inventors noted the tendency of the phosphate group of Estracyt® to dissociate in blood and thought of using the cloride group in the nitrogen mustard (III). Namely, we thought that Estracyt® cound be bound chemically to microfine particles by introducing into their surface certain functional groups capable of binding with the chloride group in the nitrogen mustard. We learned that microfine particles suitable as the carrier to which Estracyt® is bound are those which have such functional groups as -CHO, -OH, $-NH_2$, -COOH, -NCO, -Cl and $-CH_2\underset{\diagdown\,\diagup}{CH}-CH_2$ (O).

Various methods are known for making the microfine particles suitable for the purposes of the present invention. At the same time, many compounds or materials can be used as

carriers for Estracyt®. Polymerizable vinyl monomers such as acrylic acid, methacrylic acid, their esters, acrolein, glycidyl acrylate are converted to microfine particles either by emulsion polymerization or suspension polymirization in the presence of a polymerization catalyst or under the action of light or ionizing radiation. If necessary, similar vinyl monomers may be grafted onto the resulting particles. Synthetic polymers such as polyvinyl chloride, ethyl cellulose, and vinyl chloride/vinyl acetate copolymer are dispersed in a suitable medium or may be surface-treated with a suitable compound having reactive functional groups. Proteins such as albumin, globulin and hemoglobin are converted to microfine particles by denaturation with heat or radiation. Gelatin is converted to microfine particles by coacervation with the aid of gum arabic. Polyamino acids are first dissolved in solvents, then dispersed in a suitable medium for making the desired microfine particles. If necessary, polyamino acids or other monomers having functional groups may be coated onto the resulting microfine particles. Ribosome may also be converted into microfine particles by a known method. Polyisocyanates can be treated by the same method as used for polyamino acids. The objects of the present invention can be achieved by chemically binding the chloride group in Estracyt® to the mictofine particles having suitable reactive functional groups. Therefore, any type of microfine particles can be used irrespective of their source (i.e. synthetic or natural polymers), the specific method of their preparation, or their type (i.e. biodegradable

or non-biodegradable). There is also no particular limitation on the particle size. However, in consideration of their administration through blood vessels, the microfine particles are generally smaller than 100 μm, preferably between 0.5 and 30 μm in size. The type of the carrier determines the size of the particles to be taken up by organs and the amount of their uptake. Therefore, suitable carriers should be selected in view of the specific mode of therapy and the individual differences between patients.

As already mentioned, the present inventions include two aspects, i.e. the Estracyt® bound microfine particles and Estracyt® bound, cancer control agent entrapping, slow-release microfine particles. In the former case, the microfine particles having reactive functional groups are used as the carrier for Estracyt®. In the second case, these particles are bound with Estracyt® after a suitable cancer control agent is entrapped in the particles.

The following cancer control agents can be used in the present invention.

(1) Alkylating agents: These agents have in common the ability to form covalent linkages with various substances, including such important moieties as phosphate, amino, sulfhydryl, hydroxyl, carboxyl, and imidazole groups, in biologically vital macromolecules. The key biological compound affected is the purine base, guanine, in the nucleic acids of deoxyribonucleic acid (DNA), in which an alkyl group is substituted for the hydrogen on the N-7 (alkylation). Typical alkylating agents are cyclophosphamide, chlorambucil,

melphalan, thiotepa and carmustine.

(2) Antimetabolites: This group of compounds is antagonistic to normal metabolites essential for the synthesis of DNA. They compete with and displace the substrate of specific enzymes involved in DNA synthesis. The reaction between the antimetabolite and the enzyme interferes with the synthesis of nucleic acid for DNA production and therefore inhibits cell reproduction. Common antimetabolites include methotrexate, 6-mercaptopurine, 5-fluorouracil, arabinosylcytosine and cytarabine.

(3) Antibiotics: These compounds, which are chemical substances produced by certain microorganisms, suppress the growth of or destroy other microorganisms, and are also being used as antagonists of cancer cells. Commonly used antibiotics include mitomycin C, bleomycin sulfate, daunomycin, daunorubicin hydro-chloride, doxorubin hydrochloride, and mithramycin.

(4) Plant alkaloids: Included within the group of these compounds are vinblastine sulfate and vincristine sulfate.

(5) Hormones: These agents are employed to manipulate the hormonal environment of endocrine-dependent cancers such as those of the breast, ovary, and prostate. Typical hormones used as cancer control agents are adrenocorticosteroids and sex hormones.

(6) Miscellaneous: Examples are 864T, guanylhydrazone, L-asparaginase, procarbazine hydrochloride, PC-B-45, Mitotane and hydroxycarbamide.

Any substance that exhibits the cancer control

activity may be used in the present invention and can be entrapped in the Estracyt® bound microparticles.

The Estracyt® bound particles of the present invention are produced by chemically binding the chloride group of Estracyt® to the reactive functional groups on the microfine carriers listed above in the presence of amine catalysts such as ethylenediamine, and glutaraldehyde and formalin. The amount of Estracyt® to be bound to one microfine particle varies with the binding conditions and should be properly determined by the specific mode of the intended therapy.

The so prepared Estracyt® bound microfine particles of the present invention retain the target-seeking property (selective takeup by prostate related organs) and the pharmacological effect of Estracyt® to cause the prostate related organs to waste away. If these particles have a cancer control agent entrapped therein, they are also capable of treating the specific cancer tissue more effectively. Therefore, these effects of the Estracyt® bound microfine particles can be used in cancer control which is the final goal of the present invention.

The Estracyt® bound microfine particles of the present invention are typically administered transvascularly and are taken up by prostate related organs through the blood circulation. The cancer control agent entrapped in the particles can positively inhibit the growth of the specific cancer tissue with minimum systemic side effects such as vascular disorders. Once introduced into the blood vessels, the Estracyt® bound microfine particles of the present

invention are taken up by prostate related organs and exhibit the atrophic effect on these organs for several months. In cancer control therapy, this atrophic effect is equivalent to the inhibition of the cancer tissue. This pharmacological effect is interesting indeed because the conventional cancer control regimen requires daily administration of the cancer control drug either by the oral route or by injection. If Estracyt® is bound to biodegradable microfine particles, its pharmacological effect depends on how soon the carrier is decomposed and therefore, the duration for which it exhibits the desired pharmacological effect varies with the type of the biodegradable carrier. However, if Estracyt® is administered orally or by injection, it must be used daily in an amount of 300-600 mg in order to exhibit its intended effect. On the other hand, according to the present invention, satisfactory clinical results can be achieved by using 300-800 mg of the microfine particles to which 0.0001-10 mg of Estracyt® is bound. Furthermore, these particles need be administered once in order to exhibit the intended pharmacological effect for a prolonged period.

The advantages of the present invention are hereunder described in greater detail by reference to working examples. In these examples, the efficiency of Estracyt® uptake by organs was by counting the number of microfine particles present in the boiling concentrated HNO_3 solution of the organs that were removed a given period after the administration of the particles. The efficiency was indicated as a relative value, with the number of the initially administered

particles taken as 100. Qualitative determination of the uptake was also made by observation under an electron microscope. The atrophic action of Estracyt® was determined by comparing the size of the treated prostate related organs (i.e. ventral prostate, dorsolateral prostate, seminal vesicle and testicles) with untreated organs. The animals tested were male Wister strain rats weighing 400-450 g which were administered 40 mg of the Estracyt® bound microfine particles or Estracyt® bound, cancer control agent entrapping, slow-release microfine particles through femoral blood vessels. Both types of the microparticles were prepared by adding 10 mg of Estracyt® to 1 ml of a 30% aqueous solution of the microfine particles of a carrier.

Example 1

A mixture (30 ml) of glycidyl methacrylate and trimethylolpropane trimethacrylate (8:2) was dispersed in 70 ml of a 100% aqueous solution of polyvinyl alcohol (PVA), and the resulting dispersion was irradiated with gamma-rays from Co^{60} in an nitrogen atmosphere to give a total dose of 1.5×10^6 rad. The polymer particles produced (1-10 µm in size) were dispersed in a phosphate buffer solution (PBS; pH 7.4) and 10 mg of Estracyt® was added to 1 ml of PBS containing the polymer particles at a concentration of 30%. At a controlled temperature of 4°C, 0.05 ml of ethylenediamine and an equal amount of water-soluble carbadiimide were added to the solution. After effecting the binding reaction for a given period, the Estracyt® bound polymer particles were separated by centrifuge and washed with PBS.

These particles were administered to Wistar strain rats in an amount of 30 mg. A week later, the rats were slaughtered and various organs were removed to check for their uptake of the Estracyt® bound polymer particles and the pharmacological effect of Estracyt®. The results are shown in Table 1. The same procedure was followed for another group of Wistar rats (control) except that no Estracyt® bound polymer particles were administered. The average sizes of the Estracyt® bound particles taken up by the ventral prostate, dorsolateral prostate and seminal vesicle were 1 µm, 10 µm and 3 µm, respectively.

Example 2

Fine particles (<1 µm) of 5-fluorouracil (5-FU) were dispersed in 0.5 ml of a comonomer the same as used in Example 1. Thereafter, 5 ml of a 1% aqueous solution of PVA was added and a uniform dispersion was prepared. It was then irradiated with gamma-rays from Co^{60} at -78°C to give a total dose of 1.2×10^6 rad. As a result, 70% of 5-FU was entrapped into the polymer particles. To these 5-FU entrapping polymer particles were chemically bound Estracyt® as in Example 1. The particles (5-30 µm) were then administered to Wistar strain rats in an amount of 40 mg. Two weeks later, the rats were slaughtered and organs were removed. The organs were stained with hematoxylin eosin and checked for the uptake of the Estracyt® bound particles and the damage by 5-FU under an electron microscope. The results are shown in Table 1. The tissue of the dorsolateral prostate from each rat was in a complete necrotic state, indicating the effectiveness of 5-FU. The necrosis in the

ventral prostate and seminal vesicle was clearly visible to the naked eye. The blood parameters of the tested rats indicated the complete absence of side effects due to the administration of Estracyt® bound particles.

Example 3

A purified acrolein was subjected to block polymerization by irradiation with gamma-rays from Co^{60} at room temperature in a nitrogen atmosphere at a dose rate of 5×10^5 rad/hr. The resulting polyacrolein particles (1-20 µm) were dispersed in water at a concentration of 30%. To 1 ml of the aqueous solution, 10 mg of Estracyt® was added and chemically bound to the surface of the polyacrolein particles in the presence of an amine catalyst. The Estracyt® bound particles were then administered to Wistar strain rats and checked for their uptake by organs and the atrophic effect of Estracyt®. The results are shown in Table 1. The dorsolateral prostate took up a great number of 15 µm particles and the seminal vesicle took up many 10 µm particles. However, a microscopic observation revealed that the number of the polymer particles taken up by the ventral prostate was not as great as in these organs. In Example 3, the rats were slaughtered 5 weeks after the administration of the particles.

Example 4

The procedure of Example 3 was repeated except that the acrolein was replaced by an acrolein monomer containing 10% trimethylol-propane tri-methacrylate and that the irradiation with gamma-rays was effected for 20 hours at

a dose rate of 5×10^3 rad/hr. The results are shown in Table 1.

Example 5

A mixture of 30 ml of 2-hydroxyethyl methacrylate/acrylic acid/butyl acrylate (10/3/1), 200 mg of sodium dodecyl sulfate and 70 ml of water was subjected to emulsion polymerization by irradiation with gamma-rays from Co^{60} for 10 hours (dose rate: 2×10^4 rad/hr) at room temperature in a nitrogen atmosphere. The resulting polymer particles were dispersed in water at a concentration of 30%. Estracyt® (10 mg) was added to 1 ml of the aqueous polymer dispersion and chemically bound to the surface of the polymer particles in the presence of a trace amount of an amine catalyst. The Estracyt® bound particles (0.1 - 1 µm) were administered to Wistar strain rats, which were slaughtered 3 weeks later. The results of the measurements of the uptake of the particles and the atrophic action of Estracyt® are shown in Table 1.

Example 6

Microcapsules of gelatin/gum arabic were prepared by the method of coacervation using olive oil as a core material which was described in S. Miyano and A. Kondo; Journal of the Chemical Society of Japan, Industrial Chemistry Section, 73 1755 (1970). The resulting microcapsules (10 - 30 µm) were dispersed in water at a concentration of 30%. Estracyt® (10 mg) was added to 1 ml of the aqueous dispersion and bound to the surface of the capsules in the presence of trace amounts of an amine catalyst and

glutaraldehyde. The Estracyt® bound microcapsules were washed and administered to Wistar strain rats. The uptake of the microcapsules by organs and the atrophic action of Estracyt® were checked as in Example 5. The results are shown in Table 1. In Example 6, the rats were slaughtered 3 days after the administration of the Estracyt® bound microcapsules.

Example 7

Microcapsules were prepared as in Example 6 except that a mitomycin (MMC) powder was dispersed in olive oil. Each capsule contained about 10% of MMC per gram. The uptake of the microcapsules (10 - 30 µm) by organs and the atrophic action of the capsules were checked as in Example 6. The results are shown in Table 1. In this example, the rats were slaughtered 3 days after the administration of the capsules. The prostate related organs that had taken up the microcapsules experienced necrosis, indicating the atrophic action of MMC. The blood parameters of the tested rats indicated the complete absence of side effects due to the administration of the microcapsules.

Examples 8 and 9

Ten grams of bovine gamma-globulin (Example 8) or bovine albumin (Example 9) were added to 200 ml of water together with a small amount of a defoaming agent. An emulsion was made from the mixture by adding 20 ml of olive oil and heated at 80°C to produce microcapsules (1 - 100 µm) using olive oil as the core material. The microcapsules were dispersed in water to give a concentration

of 30%. Estracyt® was added to 1 ml of the aqueous dispersion and chemically bound to the surface of the microcapsules in the presence of trace amounts of an amine catalyst and formalin. The Estracyt® bound microcapsules were washed and administered to Wistar strain rats. Two days later, the rats were slaughtered and checked for the uptake of the microcapsules and the atrophic action of Estracyt®. In both examples, the microcapsules were taken up by only the ventral prostate, dorsolateral prostate and seminal vesicle. However, no appreciable atrophic action was observed. Another group of Wistar rats that were administered the Estracyt® bound microcapsules were slaughtered 4 weeks later. No microcapsule was present in the ventral prostate, dorsolateral prostate and seminal vesicle, probably because the capsules experienced biodegradation.

Example 10

Microcapsules were prepared as in Example 8 except that 5-FU particles (<1 µm) were dispersed in olive oil. Each capsule contained 8% of 5-FU per gram. The so prepared microcapsules were administered to Wistar strain rats and slaughtered 3 days later to check for the uptake of the microcapsules and the atrophic action of 5-FU. The results are shown in Table 1. The uptake data was the same as in Example 8. The ventral prostate, dorsolateral prostate and seminal vesicle suffered serious necrosis due to 5-FU. The blood perameters of the tested animals indicated the complete absence of side effects including disorders to the organs other than the prostate related organs. This suggests

the target-seeking property of the microcapsules prepared in Example 10. The same is true with the microfine particles of Example 2 and microcapsules of Example 7.

Examples 11 and 12

A mixture of 1 g of bleomycin hydrochloride particles (<20 μm), 2 g of 4% polyvinyl chloride in tetrahydrofuran and 30 ml of triethylamine (Example 11) or a mixture of the same bleomycin hydrochloride particles, 2 g of 3% ethyl cellulose in ethylene dichloride and 30 ml of heptacosafluorotributylamine (Example 12) was thoroughly agitated to form a uniform dispersion. Using this dispersion, bleomycin hydrochloride particles encapsulated with vinyl chloride (Example 11) or ethyl cellulose (Example 12) were prepared. The solvents were evaporated by stirring the dispersion at a suitable speed. For more details of the procedure for making the microcapsules of bleomycin hydrochloride, see USP 3,732,172 issued to J. A. Herbig and J. F. Hanny in 1973. In Example 11, Estracyt® was chemically bound to the polyvinyl particles in the presence of ethylenediamine. In Example 12, Estracyt® was similarly bound to ethyl cellulose particles in the presence of glutaraldehyde and ethylenediamine except that the ethyl cellulose particles had been treated with BrCN.

The microcapsules (1 - 30 μm) containing bleomycin hydrochloride were administered to Wistar strain rats. They were slaughtered one week later in Example 11, and on the third day in Example 12. The results of determination of the uptake of the microcapsules and the atrophic action

of bleomycin hydrochloride are shown in Table 1. As in Example 10, the prostate related organs that took up the microcapsules suffered serious necrosis due to bleomycin hydrochloride and no abnormality that suggested side effects was found in the blood parameters of the animals tested.

Example 13

One gram of 3% poly(γ-benzyl-L-glutamate) in ethylene dischloride was dispersed in 50 ml of 30% aqueous gum arabic in a suitable solvent, and fine particles of the polyglutamate were prepared. Estracyt® was chemically bound to the particles (1 - 30 μm) in the presence of trace amounts of amine catalyst and formalin. The resulting Estracyt® bound particles were administered to Wistar strain rats which were slaghtered 3 days later and checked for the uptake of the microparticles and the atrophic action of Estracyt®. The results were the same as in Example 6.

Example 14

Methyl methacrylate was subjected to radiation-initiated emulsion polymerization so as to prepare fine polymethyl methacrylate (PMMA) particles (0.1 - 3 μm). Acrylic acid was grafted to these PMMA particles by radiation-initiated polymerization. Eastracyt® was bound to the graft polymer particles in the presence of an amine catalyst. The resulting Estracyt® bound polymer particles were administered to Wistar strain rats. The uptake of the microparticles and the atrophic action of Estracyt® were checked. The results were similar to those obtained

in Example 3.

Example 15

Estracyt® was bound to the surface of ribosome particles in the presence of an amine catalyst and glutaraldehyde. The so prepared Estracyt® bound particles were administered to Wistar strain rats which were slaughtered 6 hours later. Observation under an electron microscope showed that the Estracyt® bound ribosome particles were taken up by only the ventral prostate, dorsolateral prostate and seminal vesicle.

Example 16

Arabinosylcytosine was bound to ribosome particles by the method described in E. Mayhew, D. Papahadjopoulos and C. Dave; Cancer Res., 36 4406 (1976). The particles were subsequently treated as in Example 15 and administered to Wistar strain rats. Twenty-four hours later, the rats were slaughtered and checked for the uptake of the particles and the atrophic action of arabinosylcytosine. The results were similar to those obtained in Example 10.

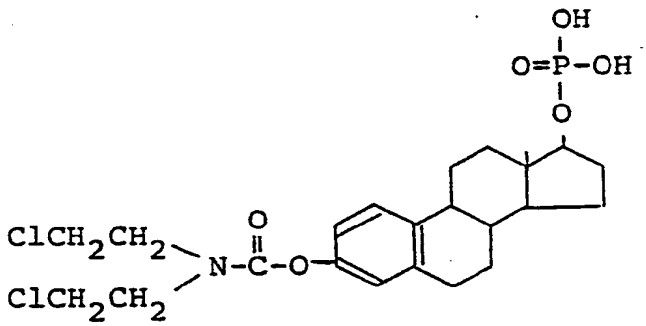
Table 1

	Uptake of Estracyt^{R} bound particles				Atrophic effect (mg/100g body weight)		
	ventral prostate	dorsolateral prostate	seminal vesicle	A B C D E F G H I	dorsolateral prostate	seminal vesicle	ventral prostate
control	-	-	-	- - - - - - - - -	262.11	618.27	98.14
Ex. 1	30%	10%	50%	- - - - - - - - -	92.02	241.38	31.82
Ex. 2	5%	60%	30%	- - - - - - - - -	21.11	41.45	6.05
Ex. 3	minimum	maximum	moderate	- - - - - - - - -	77.14	102.11	26.42
Ex. 4	20%	40%	35%	- - - - - - - - -	60.22	110.29	31.11
Ex. 5	30%	30%	35%	- - - - - - - - -	55.14	98.12	25.22
Ex. 6	uniformly distributed			- - - - - - - - -	201.14	564.33	74.99
Ex. 7	uniformly distributed			- - - - - - - - -	140.99	287.41	42.98
Ex. 10					101.43	204.24	34.14
Ex. 11	15%	40%	30%	- - - - - - - - -	76.14	180.11	20.14
Ex. 12	uniformly distributed			- - - - - - - - -	102.14	284.98	42.44

Key to the abbreviations: A: testicles, B: liver, C: kidney, D: lung, E: heart, F: pituitary gland, G: hypothalamus, H: pancreas, I: spleen

What is claimed is:

1. Target-seeking microfine particles wherein estradiol-3N-bis-(2-chloroethyl)-carbamate-17β-phosphate of the formula shown below is bound to the reactive site of a carrier particle having at least one functional group selected from the group consisting of -CHO, -Cl, $-NH_2$, -COOH, -OH, -NCO and $-CH\text{-}CH-$ (epoxy):



2. Target-seeking and slow-release microfine particles wherein estradiol-3N-bis-(2-chloroethyl)-carbamate-17β-phosphate of the formula indicated above is bound to the reactive site of a carrier particle having a cancer control agent entrapped therein and which has at least one functional group selected from the group consisting of -CHO, -Cl, $-NH_2$, -COOH, -OH, -NCO and $-CH\text{-}CH-$ (epoxy).

3. Microfine particles according to Claim 1 or 2 which have a size between 0.01 and 100 μm.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE83/00440

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC 3

A 61 K 9/14, 9/50

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
IPC 3	A 61 K 9/14, 9/50; A 61 K 31/66, 31/565; C 08 G 69/42; A 61 K 39/44
US Cl	424: 14

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [5]

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	EP, A, 0 040 506 (TEIJIN LIMITED) 25 November 1981 & JP 57009724 US 4385169 JP 57005721 JP 57018727 JP 57031930	1-2
A	JP, A, 55-85516 (NIPPON GENSHIRYOKU KEN-KYUSKO) 27 June 1980	1-2
A	DE Angew. Chem. Vol 93 (1981) p 311-332	1-2
A	GB, A, 1 436 355 (P SPEISER) 4 December 1973	1-2

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [3]	Date of Mailing of this International Search Report [3]
1984-03-06	1984 -03- 14
International Searching Authority [1]	Signature of Authorized Officer [20]
Swedish Patent Office	Tertti Gjerer Tertti Gjerer

Form PCT/ISA/210 (second sheet) (October 1981)